



Visible-light photo-catalytic C–C bond cleavages: preparations of *N,N*-dialkylformamides from 1,2-vicinal diamines



Yaohong Zhao, Shunyou Cai, Jing Li, David Zhigang Wang*

Key Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen University Town, Shenzhen 518055, China

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ABSTRACT

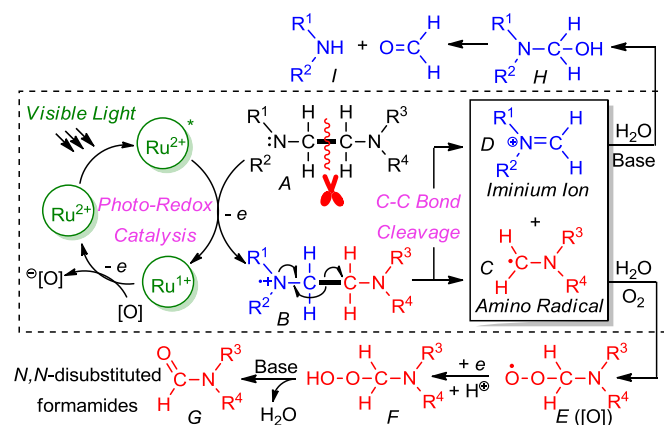
A range of 1,2-vicinal diamines were smoothly converted into *N,N*-dialkylformamides under the synergistic actions of Ru(bpy)₃Cl₂ photo-catalyst, 45 W household lighting bulb, and Cs₂CO₃ basic additive under very mild reaction conditions. The process involves visible light-enabled photo-catalytic cleavage of C–C bond as the strategic event.

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1. Introduction

Visible-light photoredox catalysis has in recent years emerged as a viable synthetic technology with increasingly wide scopes and robust reactivities.^{1–5} We had previously recorded some of the first rare examples of visible light-enabled photo-catalytic cleavages of considerably inert carbon-carbon (C–C) bonds in a range of 1,2-vicinal diamines with the aid of a commercially readily available photo-sensitizer (i.e., photo-catalyst) Ru(bpy)₃Cl₂, which upon contacting with nucleophilic nitro-compounds, further leads to synthetically attractive aza-Henry reactivities.⁶ As outlined in Scheme 1, the transformation mechanistically initiates on photo-oxidation of 1,2-diamine substrate **A**, the cationic nature of this generated species **B** then stimulates electronic fragmentation to yield simultaneously amino radical **C**, and iminium ion **D**, two apparently widely useful intermediates in organic synthesis.⁷

While the iminium ion pathway was evidently responsible for the previously disclosed aza-Henry reactivities, it is the subject of the present work to examine if the fate of in situ formed amino radical could be diverted to purposes of synthetic values. A potential reaction design concept (Scheme 1) was that upon exposing the reaction to water, base, and dioxygen atmosphere, the amino radical would be intercepted by O₂ to produce a new peroxide



Scheme 1. Visible-light-enabled photo-catalytic cleavages of C–C bonds in 1,2-vicinal diamines: the iminium ion and amino radical pathways-inspired reaction design concept.

radical **E**, which should subsequently function as the oxidant for regenerating Ru(II)-pre-catalyst from its Ru(I) precursor. Consequently, the reduced hydroperoxide species **F** would undergo base-induced dehydration event to give *N,N*-disubstituted formamide product **G**, a type of useful structures that are otherwise difficult to access with known technologies.⁸ Within this mechanistic scenario, the corresponding iminium ion **D** would be trapped by water to give a labile *N,O*-hemiacetal **H** that eventually collapse under

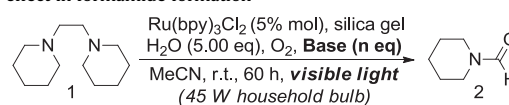
* Corresponding author. Tel.: +86 755 26035307; fax: +86 755 26032702; e-mail address: dzw@pkusz.edu.cn (D.Z. Wang).

basic condition to furnish amine **1** and formaldehyde. We reported here that with the aid of a carefully chosen (*vide infra*) base, this design concept was found to indeed correspond to experimental reality, thereby providing a new and efficient methodology for the preparations of a series of structurally variable formamide-type substances.

2. Results and discussion

With the uses of 5 mol % of Ru(bpy)₃Cl₂ photo-catalyst (in the commercially available hexahydrate form), 45 W household lighting bulb, 5.0 equiv of externally added water and an O₂ balloon atmosphere, our initial reaction conditions screenings performed on a standard vicinal diamine substrate **1** in MeCN solvent (60 h stirring at room temperature) quickly uncovered a remarkable base effect. As summarized in Table 1, the NMR internally calibrated-yield of the desired product **2** was found to be sensitively dependent on the nature of the base employed. Organic tertiary amine-type base DBU⁹ of 3.0 equiv was shown to be a poor choice, but the reaction with NaOH (3.0 equiv) demonstrated a significant improvement (47% yield of **2**). A few other inorganic bases were thus examined and the results were as following: KOH (16%), K₂CO₃ (49%), Cs₂CO₃ (81%). Clearly, Cs₂CO₃ emerged as the superior additive. When Cs₂CO₃ was used at reduced loading of 1.0 equiv, the product yield was further enhanced to be nearly quantitative (97%), while fewer amounts (0.5 equiv) were found to incur a significant yield decrease to 6.9%. It is important to note that this optimized protocol is readily amendable for scaling up without compromising the efficiency, and the transformation of **1**→**2** was conducted at gram-scale and the yield of isolated material was 90%. It also merits commenting that in complete accord with our design concept, when a less volatile vicinal diamine 1,2-bis(4-phenylpiperidin-1-yl) ethane (i.e., the substrate **3h** shown below in Scheme 2) was employed in place of **1**, both of the product **4h** and the amine 4-phenylpiperidine corresponding to the iminium ion pathway product **1** were obtained in ~1/1 molar ratio and in 90% combined yield.

Table 1
The base effect in formamide formation

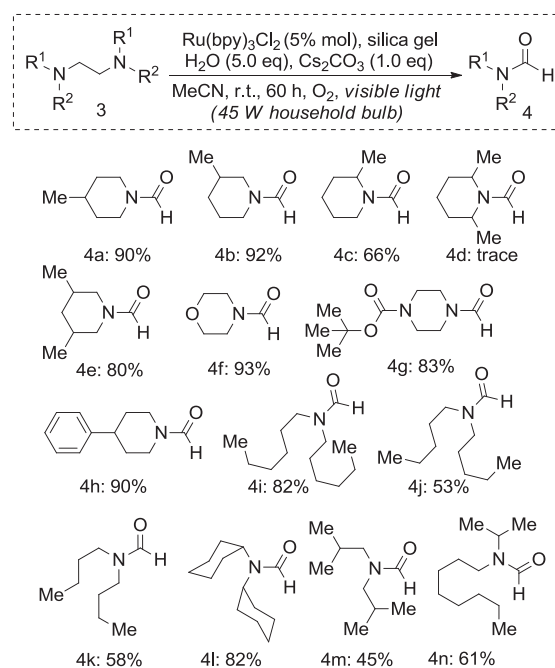


Base	DBU	NaOH	KOH	K ₂ CO ₃	Cs ₂ Cs ₂ CO ₃	Cs ₂ CO ₃	Cs ₂ CO ₃
<i>n</i> (equiv)	3.0	3.0	3.0	3.0	3.0	1.0	0.5
Yield ^a	Trace	47%	16%	49%	81%	97%	6.9%

Gram-scale preparation of **2** accomplished at 90% isolated yield.

^a Yields were determined by ¹H NMR using naphthalene as an internal standard.

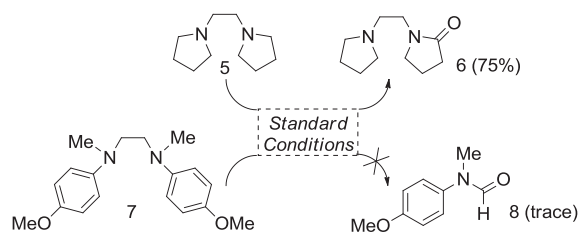
A list of 1,2-diamine substrates generally structured as **3** were next subjected to the above identified optimal reaction conditions, and the results, as compiled in Scheme 2, evidently demonstrated a considerably general scope.¹⁰ Piperidine-derived amide products **4a**–**4b** bearing γ- or β-methyl group were produced in similar isolated yields (90% and 92%, respectively), and their α-methylated analog **4c**, presumably due to the interference of steric hindrance, was furnished in a much lower yield (66%). The unfavorable size influence escalated further with the extreme bulky **3d**, in which the production of **4d** was practically inhibited. A release of such steric congestion simply by relocating the two α-dimethyl substitutions to neighboring β-positions in **4d** immediately resumed the reactivity, leading to product **4e** in 80% yield. Morpholine and piperazine-derived structures were well accommodated, and their products **4f** and **4g** were furnished in 93% and 83% yields, respectively. These results were notable in that the lone pair



Scheme 2. Survey of reaction scope.

electronic densities of oxygen and nitrogen-atoms in the substrates do not seem to interfere with their photo-oxidation events. γ-Phenyl-substituted piperidine amide **4h** was obtained in 90% yield. Furthermore, purely acyclic vicinal diamines, either symmetrically (**3i**–**3m**) or unsymmetrically substituted (**3n**), were all shown to be competent substrates, and their corresponding formamides **4i**–**4n** were uneventfully isolated in moderate-to-high yields (45–82%).

The above-described ‘standard’ protocol was found to nevertheless be non-suitable for strained cyclic or aryl-substituted 1,2-vicinal diamines. Presented in Scheme 3 are preliminary not the anticipated formamide, but a new amide **6** in 75% yield bearing an intact skeleton! The formation of **6** may best be rationalized by base-promoted auto-oxidation¹¹ of the in situ formed *N,O*-hemiacetal species. For aryl-substituted diamine **7**, only trace amount of formamide product **8** was detectable, suggesting the inefficiency of an aryl-stabilized amine radical cation (i.e., species **B**) towards further electronic fragmentation. Expanding the current methodology’s arena to these substrate types must therefore await further experimental investigations.



Scheme 3. Notable experimental observations.

3. Conclusion

In summary, we disclosed herein a remarkably simple and mild protocol for converting a range of structurally variable 1,2-vicinal diamines to the *N,N*-dialkyl substituted formamides. The apparent values of this discovery leverage on three complementary facts that there are currently rather limited methods known for preparations of formamides that the starting materials employed herein are

economically abundantly available, and that the conditions used are exceptionally mild and readily implementable. It is therefore our hope that the finding would attract attention from and find further utilities by practicing chemists.

4. Experimental

4.1. General experimental

Reagents were purchased at the highest commercial quality from Acros and Aldrich and used without further purification unless otherwise noted. Silica gel (ZCX-II, 200–300 mesh) used for flash column chromatography was purchased from Qing Dao Ocean Chemical Industry Co. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III (300 MHz, 400 MHz or 500 MHz) spectrometers and are internally referenced to residual solvent signals (note: CDCl_3 referenced at δ 7.26 ppm for ^1H and δ 77.0 ppm for ^{13}C). Data for ^1H NMR are reported as follows: chemical shift (δ parts per million), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, dd=doublet of doublets, ddd=doublet of doublet of doublets, and m=multiplet), integration, coupling constant (Hertz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). High resolution mass spectrometric (HRMS) data were obtained using Bruker Apex IV RTMS. High performance liquid chromatography (HPLC) was performed on a Shimadzu LC-20A using Daicel Chiralcell[®] chiral columns (25 cm) and guard column (5 cm) as noted for each compound. The room temperature (294 ± 1 K) single-crystal X-ray experiments were performed on a Bruker P4 diffractometer equipped with graphite monochromatized Mo K_α radiation. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. For full experimental details, including procedures for all reactions and characterizations of all new compounds (chiral HPLC analysis, ^1H NMR, ^{13}C NMR, mass spectrometry), X-ray single crystal structure analyses, see the Supplementary data.

4.2. General procedure for visible-light photo-catalytic C–C cleavage to prepare *N,N*-dialkylformamide from vicinal diamine

A flame-dried round bottom flask (10 mL) was equipped with magnetic stir bar and charged with diamine compound (0.4 mmol, 1.0 equiv), silica gel (30 mg), tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (0.02 mmol, 0.05 equiv) and MeCN (4.0 mL). To the mixture was then added Cs_2CO_3 (0.4 mmol, 1.0 equiv), water (2.0 mmol, 5.0 equiv), and irradiated by a household bulb (45 W) under a balloon oxygen atmosphere at room temperature until the starting material disappeared from the TLC. The reaction mixture was filtered through Celite, and the filtrate was washed with ether. After that the filtrate was concentrated under reduced pressure, the residue was purified by silica gel column chromatography to afford the desired pure product.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.tet.2013.07.056>.

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